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09/322,067	05/27/99	SPIELMAN	[illegible]

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1631	9

DATE MAILED: 04/13/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 1/31/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire Three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1 - 52 is/are pending in the application.
Of the above, claim(s) 23 - 42 (non-elected) is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1 - 22 and 43 - 52 is/are rejected.
☒ Claim(s) 6 and 7 is/are objected to.
☒ Claim(s) 1 - 52 are subject to restriction or election requirement.

Application Papers

SK ☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

The art unit designated for this application has changed. Applicant(s) are hereby informed that future correspondence should be directed to Art Unit 1631.

1. Applicants response to the restriction requirement dated January 31, 2000 is acknowledged (paper # 7). This examiner accepts the traversal arguments used by the applicants regarding groups II (claims 20-22) and IV (claims 43-52), and withdraws the election made in the prior office action. Accordingly, this examiner will examine the inventions of groups I (claims 1-19), II (claims 20-22) and IV (claims 43-52) without traverse in this office action. In addition, applicants elected to cancel claims drawn to non-elected subject matter (claims 23-42).

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a) (1) and (a) (2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because no submission of computer readable form sequences etc. has been submitted. Applicants are given the same response time regarding this failure to comply as that set forth to respond to this office action. See the sequence appearing in Figure 12/1. However, the applicants should notice that Seq. ID numbers are not required in the figure.

Specification

3. The attempt to incorporate subject matter into this application by reference to web sites is improper. **(See pages 4, 5, 8, 46, 83, 97, 100, 101, 122- 124, 126, 128, 136, 137 and 141)** Appropriate action is required.

4. Page 119 of the instant application has a punched-out portion at the top of Table 9. This examiner requests a replacement page from applicants.

Claim Objections

5. Claims 6 and 7 are objected to because they include abbreiviation characters which are not enclosed within parentheses and are not defined in the claims. Appropriate action is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The applicants did not describe anywhere in the instant application how one can use and apply the method of instant claims 1-22 without a "computer." To that end, instant claims 1-22 are not enabled without it.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 3-10, 12, 15-22, and 43-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Holm et al. "An evolutionary treasure: Unification of a broad set of amidohydrolases related to urease." PROTEINS: Structure, Function and Genetics 28, 72-82 (1997). **(See the entire paper).**

Holm et al discloses and exemplifies a novel procedure for the definition and prediction of functional site descriptor(s). (Notice that one skilled in the art understands that a functional site descriptor(s) means, for example, the amino acid residues present in an enzyme active site, or as we will discuss below, the metal centers and the first shell of ligands attached to them in a metalloenzyme that performs the protein function.) Taking urease as an example, Holm et al used the three dimensional structure of urease (**obtained from its X-ray crystal structure at 2 A resolution**) to discover strong similarities of enzyme architecture to adenosine deaminase and

phosphotriesterase, which has gone undetected by one dimensional sequence comparisons. **(Notice that the X-ray crystal structure of the latter two enzymes are also known to within less than 3 A resolution.)** In addition, based on **a three-dimensional analysis of conservation patterns**, Holm et al further discovered similar active-site architecture in an even larger set of enzymes involved in nucleotide metabolism. Their discovery of the latter groups of enzymes included their **three-dimensional fold and details of the active site(s) architectures.** Using urease, phosphotriesterase and adenosine deaminase as examples, **the automated procedure** used by Holm et al can be summarized as follows (Holm et al pp.73-75):

(a) Structure Alignment: The **three dimensional** structures of urease, phosphotriesterase and adenosine deaminase were aligned structurally **(without reference to the amino acid sequences)** using the Dali program (See Holm et al, Figure 1 p. 74, especially the figure legend). The evolutionary constraints common to the three enzyme families are (i) a precisely defined histidine-aspartic acid signature required for metal binding and catalysis, and (ii) a structural context of alternating alpha-helix and beta-strand secondary structure elements in which the functional residues map to the C-terminal end of strands 1, 5, 6 and 8. **(b) Walking in Sequence Space:** Holm et al describes an efficient way for exploring the amino acid sequence space between and around structurally identified members of an emerging superfamily. Their approach is based on **pairwise comparisons of proteins to identify candidate sequences and profile**. A walk in sequence space starts from a seed sequence and uses **standard** search tools (FASTA with optimized scores and searching a nonredundant database of protein sequences) to collect **first**

neighbors, and then branches out collecting **second** neighbors, that is, those of peripheral members, **third** neighbors **and so on.** (See Holm et al, Figure 4, p. 79). **(c) Analysis of Conserved Patterns/Functions** Holm et al set FASTA cutoff for statistically significant links to 0.01 expected hits in a nonredundant protein database of 207,645 sequences. Then, the evolutionary constraints describing the new candidate families were analyzed from alignments generated by progressive alignment. **Automatic programs** were used to align closely related sets of sequences. The multiple alignments were used as input for **secondary structure predictions** for each family by **linear discrimination function and neural network methods**. (See Holm et al, Figures 2 and 3 pp. 76-78). The signature patterns were identified by inspection of conservation patterns within families. **Threading the sequences onto the known 3D structures** phased on the active site pattern preserved the **hydrophobicity of the structural core.**

The applicants in instant claims 1 and 43 are claiming " a functional site descriptor that defines a spatial configuration for a functional site of a protein, which functional site corresponds to a biological function other than **a divalent metal ion binding site** ..." The model of Holm et al is not restricted to metalloenzymes, where the amino acid residues attached to the metal centers are taken as the signature pattern. (See p. 79 under the heading "evolution of new cellular functions"). The model advanced by Holm et al also predicted other families in which the catalytic residues (histidine-aspartic acid) are not conserved, yet, sequence conservation remains very clear in surrounding structural positions. Holm et al discloses and exemplifies that

in those cases the subfamilies no longer function as enzymes but rather reuse the fold for another biological function. For example, lysozyme/alpha-lactalbumin, the regulatory subunit of lactose synthetase and **serine proteases**.

The applicants also in instant claims 20-22 are claiming building a library containing functional site descriptors. Due to the sizes of searched databases for finding proteins containing the functional site descriptors of interest, **(Holm et al searched a database containing ~ 207,000 sequences)**, the generated output from such database searches (hits) are always placed in a separate output file. For example, Holm et al. (See p. 75 second column in the page) built a library of their findings and made it available over the internet.

From the discussion presented *supra*, we conclude that all of the elements in instant claims 1, 3-10, 12, 15-22, and 43-50 are anticipated by Holm et al.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1-22, and 43-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al. ("Derivation of 3D coordinate templates for searching structural databases: Application to Ser-His-Asp catalytic triads in the serine proteinases and lipases." PTO 1449).

Wallace et al. **(See the entire document)** teaches and exemplifies the derivation of 3D coordinate templates for searching structural databases with specific applications to serine proteinases and immunoglobulin G1. Wallace et al exemplifies the use of Ser-His-Asp catalytic triad of the serine proteinases and lipases as a template for scanning databases (Protein Data Bank and SWISS-PROT) of known protein structures to identify putative catalytic centers. The first step in the procedure (See pp. 1004-1006 "derivation of the 3D templates") was the extraction of all occurrences of interacting Ser, His and Asp using a program called DISTRIB. Wallace et al set a criterion for interacting residues if at least **one interactomic contact was less than the sum of the van der Waals radii of the contacting atoms plus 1 A. Then, each extracted triplet was transformed onto a common reference frame defined by the planar ring of the His.** The second step was to **automatically** filter from these Ser-His-Asp triplets only those that were catalytic triads with well conserved conformations. **The used proceedure was an iterative one (See Figure 1 of Wallace et al) involving the use of the known catalytic triads as a starting point, or seed. The seed triad was Ser 195-His 57-Asp 102 from alpha-**

lytic protcinasc Ilpr. Initially, Wallace et al calculated the root-mean-square-distance (RMSD) of all Ser and Asp side chain atoms relative to the seed triad. The RMSD cut-off of 2.0 A was used and DISTRIB located potential hits, which are automatically extracted and a new tcmplatc was calculated. In order to avoid biasing the results toward the largest of the fold groups (Group I in Table I), a separate mean template was calculated for each of the four fold groups and these means werc averaged to givc an ovcrall mean tcmplate. The procedure was repeated and in each cycle the 3D coordinates of the template werc refincd and new triad hits wcrc pulled until no new hits were obtained. The Final 3D template has been termed by Wallace ct al as "The Functional Template." A second template was then crcatcd called the "side chain template" and computed. The side chain tcmplatc coordinates of all the Asp and Ser side-chain atoms.

Wallace et al. make a vcry important observation in their paper (See p. 1011 "Discussion" cspecially last paragraph of the second column). Namely, the whole procedure described in their paper nceds an initial "sccd" conformation to start it off. Such a seed can be generated automatically with no prior knowledge of its functional importance. For example, for an association of residues X-Y-Z, the first such association encountered in the data set of structures could be taken as the starting seed. If sufficient matchcs were found during subsequent cycles, the template could be stored as a common triad motif that might have cithcr a functional or structural significance. Therefore, using

the Wallace et al approach, it is possible to build a database of common 3D residue motifs, much like the functional motifs used in the PROSITE database.

Wallace et al differs from the instant application in two aspects. The first, is the use of pseudo-atoms in building the seed functional site. The second diference is the use of 3-15 amino acid residues to build the functional site.

Regarding the first point, one with ordinary skill in the art of computational sciences realizes that the use of pseudo-atoms located at the center-of-mass of an amino acid side chain, or, the actual use of the coordinates of the atoms is **irrelevant to the practice of the invention**. The reason is that **the coordinates of the "seed conformation" set the reference** with respect to which the databases will be searched. (See the discussion by Wallace et al. Pertaining to the derivation of the 3D templates on pp. 1004-1006).

As to the second point, the applicants define a functional site descriptor containing up to 15 amino acids. Wallace et al in the last paragraph of his publication stated that "**the whole procedure described in their paper needs an initial "seed" conformation to start it off**" Accordingly, the initial seed can contain more than three amino acid residues to start the procedure. Therefore, it would have been obvious to one with ordinary skill in the art to apply the computer program procedure advanced by Wallace et al to functional sites containing more than 3-amino acid residues with the motivation of discovering structural and functional relationships between diverse protein families.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Sherif A. Kafafi whose telephone number is (703) 305-0509. The examiner can be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Sherif A. Kafafi, PhD

S.A. Kafafi

ARDIN H. MARSCHEL
PRIMARY EXAMINER

Art Unit 1631.

April 4, 2000